

3, 10 2
1980 82

EXECUTIVE SUMMARY

1987 FOLLOWUP MORBIDITY REPORT

The Air Force Health Study is an epidemiologic investigation to determine whether adverse health effects exist and can be attributed to occupational exposure to Herbicide Orange. The study consists of mortality and morbidity components, based on a matched cohort design in a nonconcurrent prospective setting with followup studies. The Baseline study was conducted in 1982, and the first two followup morbidity studies were performed in 1985 and 1987. The purpose of this report is to present the results of the 1987 followup.

In the Baseline morbidity study, each living Ranch Hand was matched to the first living and compliant member of a randomly selected Comparison set based on age, race, and military occupation, producing an approximate 1:1 contrast. The Comparisons had served in numerous flying organizations that transported cargo to, from, and within Vietnam but were not involved in the aerial spraying of Herbicide Orange. All previous participants and refusals, newly located study members, and replacements (matched on reported health status) were invited. Eighty-four percent (995/1,188) of the eligible Ranch Hands and 77 percent (939/1,224) of the eligible Original Comparisons participated in the 1987 followup examination and questionnaire process. Participation among those who were fully compliant at Baseline was very high. Ninety-two percent of the Ranch Hands and 93 percent of the Comparisons who were fully compliant at Baseline also participated in the 1987 followup. In total, 2,294 study subjects, 995 Ranch Hands and 1,299 Comparisons, participated in the 1987 followup.

The followup study was conducted under contract to the Air Force by Science Applications International Corporation, in conjunction with the Scripps Clinic and Research Foundation and the National Opinion Research Center. Most of the data were collected through face-to-face interviews and physical examinations conducted at the Scripps Clinic in La Jolla, California. Other data sources included medical and military records and the 1982 and 1985 data bases. As a contract requirement, all data collection personnel were unaware of each participant's exposure status, and all phases of the study were monitored by stringent quality control. The statistical analyses were based on analysis of variance and covariance, chi-square tests, Fisher's exact tests, general linear models, logistic regression, proportional odds models, t-tests, and log-linear models, all of which were specified in an analytical plan written prior to data analysis.

The questionnaire and physical examination data were analyzed by major organ system. The primary focus was on the assessment of differences between the Ranch Hand and Comparison groups based on data from the 1987 followup. Additionally, dose-response relationships within the Ranch Hand group were examined, and longitudinal assessments of differences in the changes of the two groups between the examinations were conducted for selected variables.

In the analyses in this report, Ranch Hand exposure to dioxin was quantified by use of a calculated index based on the quantity of herbicides containing dioxin sprayed each month and the number of Ranch Hands assigned to each occupational category in those months. The statistical relationships between the evaluated conditions and the calculated index were assessed for

significance and patterns suggestive of dose-response. However, early results of serum dioxin studies in Ranch Hand personnel conducted at the Centers for Disease Control indicate the calculated index is not a good measure of actual dioxin exposure. Therefore, the results of analyses using the calculated exposure index should be interpreted with caution. A full report relating the serum assay results to the medical data contained in this report is expected in 1991.

The fixed size of the Ranch Hand cohort limits the ability of the study to detect group differences, particularly for the rare occurrences of soft tissue sarcoma and non-Hodgkin's lymphoma. The study has virtually no statistical power to detect low to moderate group differences for these malignancies. The study has good power to detect relative risks of 2.0 or more with respect to disease occurring at prevalences of at least 5 percent in the Comparison group, such as basal cell carcinoma.

Self-perception of health, appearance of illness or distress, relative age, and percent body fat were similar in the two groups. There has been a decline in the percentage of individuals reporting their health as fair or poor in both groups since the Baseline examination. A significantly greater percentage of Ranch Hands than Comparisons, however, had abnormal erythrocyte sedimentation rates. Only three participants (two Ranch Hands and one Comparison) had rates in excess of 100 mm/hr. The Comparison had lung cancer and died in early 1989. In neither of the Ranch Hands was a diagnosis established during the course of the 1987 followup. A significant difference was also detected at the 1985 followup examination, and it will be important to monitor the sedimentation rates in subsequent examinations.

For all verified neoplasms combined, Ranch Hands had a significantly greater frequency than the Comparisons. Ranch Hands also had a marginally significant greater frequency than the Comparisons when suspected neoplasms were included in the analysis. Because cancers fall into systemic or skin categories, group contrasts were performed within each category. Analyses restricted to systemic neoplasms revealed no significant differences between the Ranch Hands and Comparison groups. Focusing only on skin neoplasms, Ranch Hands had significantly or marginally significant higher frequencies for the following categories: all verified skin neoplasms, all verified and suspected skin neoplasms, all verified malignant skin neoplasms, and sun exposure-related malignant skin neoplasms. Significant group differences for the sun exposure-related malignant skin neoplasms are not surprising because approximately 90 percent of the participants with those neoplasms had verified basal cell carcinomas, and Ranch Hands had significant or marginally significant higher frequencies of verified basal cell carcinoma than the Comparisons.

The neurological assessment did not disclose significant findings detrimental to the health of the Ranch Hands, although several differences were noted. Of the six reported and verified neurological diseases and disorders, the only significant finding was that Ranch Hands had a higher incidence of hereditary and degenerative neurological diseases. Unadjusted analyses for the 30 physical examination variables showed marginally more balance/Romberg sign and coordination abnormalities in the Ranch Hand group than in the Comparison group. In the adjusted analyses, a significant difference in the relative risk for the cranial nerve index (without range of

motion) occurred with insecticide exposure. Stratified results showed that among those who had never been exposed to insecticides, significantly more Ranch Hands than Comparisons were abnormal on this index. Of those who had been exposed to insecticides, the percentage of abnormalities on this index was marginally higher in the Comparisons. The adjusted analysis for coordination detected two significant group-by-covariate interactions (group-by-occupation and group-by-insecticide exposure). Stratified analyses found a significant group difference for enlisted groundcrew after excluding the group-by-insecticide exposure interaction, and a significant adjusted group difference overall after excluding both group-by-covariate interactions. Ranch Hands had significantly more coordination abnormalities than Comparisons for each analysis. The trend of increasing abnormality in the enlisted groundcrew for coordination will be more fully evaluated in the analyses of serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) levels.

The psychological assessment was based on the analysis of 52 variables, which included reported illnesses verified by medical record review, reported sleep disorders, and scores from two clinical psychological tests. The results showed that significant or marginally significant differences between the Ranch Hands and the Comparisons were found for some verified psychological disorders, reported sleep disorders, and the self-administered Symptom Checklist-90-Revised and Millon Clinical Multiaxial Inventory psychological examinations. For these differences, the Ranch Hands generally manifested higher percentages of abnormalities or higher mean scores than the Comparisons. However, this is not surprising since individuals who perceive themselves as having been harmed might be more likely to report the symptoms found to be significant in this analysis. These results will be reexamined for positive correlations between the complaints and dioxin levels when the serum assay data become available. Additionally, significant group-by-covariate interactions were frequently observed in the adjusted analysis, which often made direct contrast of the two groups with adjustment for significant covariates difficult. The covariates of age, alcohol history, and presence of post-traumatic stress disorder showed strong effects on many of the psychological measurements. There was generally a lack of consistency in the findings of similar variables in the psychological tests.

The gastrointestinal assessment found no significant group difference for historical liver disease, historical and current ulcer, and current hepatomegaly. The Ranch Hand alkaline phosphatase mean was significantly higher than the Comparison mean, but group differences for the other laboratory examination variables (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, total bilirubin, direct bilirubin, lactic dehydrogenase, cholesterol, high density lipoprotein [HDL], cholesterol-HDL ratio, triglycerides, creatine kinase, and fasting glucose) were not significant.

In the dermatologic assessment, no cases of chloracne were diagnosed. For participants with no history of acne before the start of the first Southeast Asia (SEA) tour, a greater percentage of Ranch Hands than Comparisons reported the occurrence of acne after the start of the first SEA tour. However, the anatomic pattern of these lesions was not suggestive of chloracne. No other significant group differences were detected in the remainder of the analyses. The exposure index and longitudinal analyses were also essentially negative; the few positive findings were inconsistent with

dose-response effects and the available knowledge of current serum TCDD levels in the Ranch Hand group.

The cardiovascular evaluation showed that the health of the two groups was similar for reported and verified heart disease and central cardiac function. With regard to peripheral vascular function, the Ranch Hands manifested a marginally higher mean diastolic blood pressure than the Comparisons, but the percentage of individuals with a diastolic blood pressure above 90 mm Hg was not significantly different in the two groups. The Ranch Hands had a marginally higher percentage of individuals with carotid bruits, and there were also significant, or marginally significant, differences with respect to femoral pulses, dorsalis pedis pulses, and three aggregates pulse indices (leg, peripheral, and all pulses), as assessed by manual palpation. Significantly more pulse abnormalities in the Ranch Hands were also found at Baseline, when pulses were measured by manual palpation, but not in the 1985 followup, when both manual and Doppler measurements were utilized.

In the hematologic evaluation, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were not significantly different in the two groups. The mean white blood cell and platelet counts were significantly greater in the Ranch Hands than in the Comparisons, but the magnitude of the difference was small in each case. The difference in platelet counts was significant despite that in the longitudinal analysis of the changes from Baseline to the 1987 followup examination, platelet counts in the Ranch Hands decreased to a significantly greater degree than in the Comparisons. The percentage of individuals with abnormally high platelet counts was also significantly greater in the Ranch Hand group, but the relative risk was less than 2. In addition, no platelet count was elevated into a pathologic range. Exposure index analyses did not generally support dose-response relationships.

The groups did not differ significantly in reported history of kidney disease/stones or for urinary protein, urinary occult blood, urinary white blood cell count, blood urea nitrogen, or urine specific gravity based on unadjusted analyses. In the adjusted analyses, there was no pattern of results that suggested a detriment to either group.

For the endocrinologic assessment, the Ranch Hand thyroid stimulating hormone (TSH) mean was marginally significantly higher than the Comparison TSH mean, but results of the TSH discrete analyses did not show statistically significant group differences. Mean levels for triiodothyronine percent (T_3 %) uptake, testosterone, and 2-hour postprandial glucose were similar between groups. The percentage of abnormal levels for each of these variables, and the composite diabetes indicator, was higher for the Ranch Hand group than for the Comparison group, but none of these differences was statistically significant. Self-reported data on current thyroid function and past history of thyroid disease were similar between groups. Also, the percentages of participants with thyroid or testicular abnormalities diagnosed at the physical examination were not statistically different between groups. Overall, the endocrinologic health status of the Ranch Hand group does not appear substantially different from the Comparison group.

For the immunologic assessment of the 1987 followup, Ranch Hands and Comparisons did not differ on the cell surface markers, functional stimulation

tests, total lymphocyte counts, or quantitative immunoglobulins. Statistical analyses of the natural killer cell assay variables adjusting for covariate information were conducted within the Black and nonblack strata. These analyses showed that Black Ranch Hands had higher adjusted mean counts and average percent releases than the Black Comparisons for the natural killer assay measures. The meaning of this observation is unknown. Without adjusting for covariate information, significantly more Ranch Hands had a possibly abnormal reading on the composite skin reaction test than the Comparisons. Adjusting for covariate information resulted in performing group contrasts on the composite skin reaction variable within strata of the lifetime cigarette smoking history variable. For the heavier smoking participants, significantly more Ranch Hands had a possibly abnormal reading on the composite skin reaction test than the Comparisons. Within the other strata, there were no significant differences.

The pulmonary health of the two groups was reasonably similar based on the analyses without adjustment for covariates, although the Ranch Hands had significantly more thorax and lung abnormalities and marginally higher prevalence rates for hyperresonance. When significant interactions involving group were ignored, no significant differences were found in the adjusted analyses. Exploration of the interactions did not identify a consistent pattern. The adverse effects of smoking were evident in all analyses.

The process of inferring causality is complex and must be based on careful consideration of many factors. Any interpretations of the data must consider the biological plausibility, clinical significance, specificity and consistency of the findings, and a host of statistical factors, such as strength of the association, lack of independence of the measurements, and multiple testing. Based on direct and indirect evidence, it is concluded that this study is free of overt bias and the measurement systems used to obtain the data were accurate and valid.

In summary, there is not sufficient evidence at this time to implicate a causal relationship between herbicide exposure and adverse health in the Ranch Hand group. No cases of chloracne or porphyria cutanea tarda, the two most commonly accepted effects of dioxin exposure, were detected in this study. There was a single case of soft tissue sarcoma in each group and one case of non-Hodgkin's lymphoma in a Ranch Hand. The differences noted indicate that reanalysis using dioxin body burden levels and continued medical surveillance are warranted.